PATENT SPECIFICATION (11) 1313429

NO DRAWINGS

(21) Application No. 26263/70 (22) Filed 1 June 1970

(31) Convention Application No. 852467 (32) Filed 22 Aug. 1969 in

(33) United States of America (US)

(44) Complete Specification published 11 April 1973

(51) International Classification C07D 99/16//C07C 101/02 C07D 85/04

(52) Index at acceptance

C2A 1C2A 1C2C 2C1

C2C 170—191—279 171—176—183 211 215 222 225 227 22X 22Y 255 25Y 30Y 321 32Y 351 352 364 366 367 369 36Y 386 401 40Y 45X 45Y 490 620 624 628 635 660 662 668 761 LS TQ

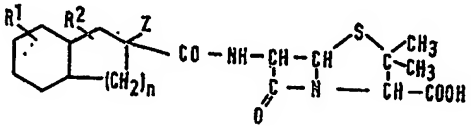
(19)

(54) PENICILLINS

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement: —

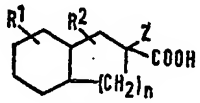
This invention relates to 6-(2-amino-hexahydro-2-indancarboxamido)penicillanic acids and 6-(1,2,3,4,5,6,7,8,9,10-decahydronaphthalene-2-amino-2-carboxamido)penicillanic acids having broad spectrum antimicrobial activity against gram-positive and gram-negative micro-organisms, i.e. bacteria, including penicillin resistant staphylococci. It also relates to processes for preparing such compounds. These penicillins are relatively acid resistant and are thereby effective on oral administration and they have low solubility which makes them useful in repository injectable dosage forms without the necessity for forming salts thereof with organic bases.

The invention provides a process for the preparation of a penicillin having the general formula



(I)

in which Z is an amino group or a protected amino group or an azido or nitro group, R^1 and R^2 are hydrogen, lower alkyl, lower alkoxy, aryl or aryloxy and n is 1 or 2, or a salt thereof in which 6-aminopenicillanic acid or a functional derivative thereof is acylated with an acid of general formula



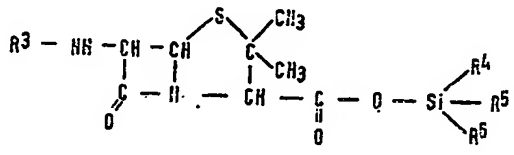
wherein R^1, R^2, Z and n are as defined above, or its functional derivative and, if desired a protecting group is removed or an azido or nitro group Z is reduced to an amino group.

In the above process, the 6-aminopenicillanic acid or a functional derivative, which includes salts and organo silyl and organosilenyl derivatives, is coupled with the amino acid, protected amino acid or its precursor by methods generally known to

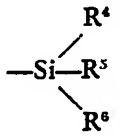
form amide bonds in peptide and penicillin chemistry. Examples are reaction with an anhydride or mixed anhydride with an organic or inorganic acid or acyl halide or functional ester (e.g. a *n*-nitrophenyl ester) derived from the acid or with the acid itself in the presence of a dehydrating or functionalising agent such as a carbodiimide (usually dicyclohexylcarbodiimide), N,N-carbonyldimidazole or an alkoxyacetylene. To prepare an anhydride the acid is treated with a dehydrating agent, to prepare a mixed anhydride it can be treated with an acylating agent derived from an organic or inorganic acid, to prepare a corresponding acyl halide the acid can be reacted with halogenating agent such as thionyl chloride, phosphorous pentachloride or phosphorous pentabromide. In carrying out such a reaction, free amino groups are protected and the protecting group is removed in known manner. To avoid the need for such protection the amino group can be generated from an azido or nitro as aforementioned by generally known methods such as catalystic hydrogenation for instance over a platinum group metal (Pt, Os, Pd, Rh, Ir, Re) or Raney nickel catalyst or electrolytic reduction or, with a nitro group, by treatment with a reducing agent. All of these reactions are carried out under conditions mild enough to avoid destruction of the penicillin nucleus. When Z is $-NH_2$ the compounds are active penicillins provided by the invention. When Z has one of the other meanings the penicillins are valuable intermediates for those where Z is $-NH_2$.

When an amino group has to be protected it is much preferred to bring this about by the use of an N-carboxyanhydride, preferably carrying out the coupling reaction under acid conditions such as pH 3—6.5 or even up to pH 8 since a separate step for removing the protecting group is thereby rendered unnecessary. However, protection can also be by any of the protecting groups known in the penicillin and peptide arts, for instance using a benzyloxycarbonyl radical which can for instance be substituted such as by halo, nitro or alkoxy in the benzene ring, particularly at the para position, a benzhydryloxycarbonyl radical, a trityl radical, an alkoxycarbonyl radical particularly *t*-butyloxycarbonyl, allyloxycarbonyl or β,β,β-trichloroethyloxycarbonyl, a sulphur containing radical such as a tritylsulphenyl, o-nitrophenylsulphenyl or other arylsulphenyl radical, or a radical obtained by reacting the free amino group with a β-dicarbonyl compound such as acetylacetone, acetoacetic esters or benzoylacetone to form enamines or Schiff bases or with an aldehyde, e.g. an aromatic hydroxyaldehyde, to form a Schiff base, or a trifluoroacetyl or *p*-tolylsulphenylethoxycarbonyl group. Protection can also be by protonation for instance as a hydrohalide or other acid addition salt. The removal of protecting groups after the coupling reaction is also well known to the art, usually by mild acid or base catalysed hydrolysis or by hydrogenolysis over a noble metal or Raney-Nickel catalyst. For instance benzyloxycarbonyl and related groups and trityl groups can be removed by catalytic hydrogenation or electrolytic reduction and a β,β,β-trichloroethyloxycarbonyl group can be readily removed by zinc in a lower alkanoic acid. In the case of sulphur containing radicals, enamines and Schiff bases the protecting group is preferably removed by mild acid hydrolysis, for instance at a pH of about 2. A tertiarybutoxycarbonyl group is also preferably removed by mild acid hydrolysis, especially with formic acid. An *o*-nitrophenylsulphenyl or related group can be removed by nucleophilic attack on the sulphur atom of the sulphenamide group for instance using an alkali metal iodide, dithionite or thiocyanate. Trifluoromethyl and *p*-tolylsulphenylethoxycarbonyl groups can be removed by mild hydrolysis with a base.

If it is desired to use a functional derivative of 6-amino penicillanic acid, silyl derivatives can be those of general formula:

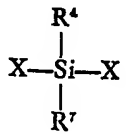


where R^3 is a hydrogen atom or the radical

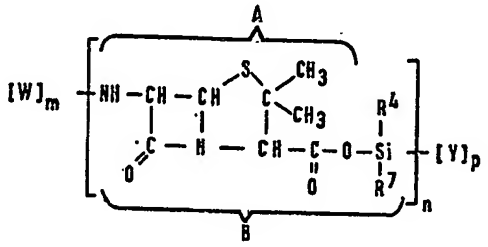


and R^4, R^5 and R^6 are the same or different and each is an alkyl, cycloalkyl, aryl, or aralkyl group and they can be prepared as is well known by reacting 6-aminopenicillanic acid with one or two molecular amounts of a corresponding substituted silyl halide, aminosilane or disilazane.

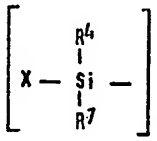
Silene derivatives of 6-aminopenicillanic acid are the polymeric derivatives prepared by reacting 6-aminopenicillanic acid with a substituted silyl di- or trihalide of general formula:



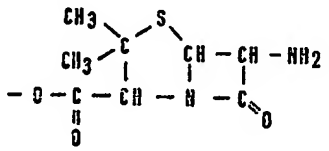
where X is a halogen, R^4 is as defined above or halogen, and R^7 is hydrogen, alkyl, cycloalkyl, aryl or aralkyl. The silene derivatives obtained have the general formula:



where R^4 and R^7 are as defined above, W is hydrogen or a radical of the formula



where X, R^4 and R^6 have the above meanings, m is 0 or 1, n is an integer from 1 to 25, p is 0 or 1 and Y is halogen or a group of general formula



with the provisos that:

(a) when m is 0 and p is 0, n is more than 1 and the two free valencies are joined together to complete a cyclic compound,

(b) when n is more than 1, the moieties A of the additional groups B recur in random head-to-head, tail-to-tail and head-to-tail disposition,

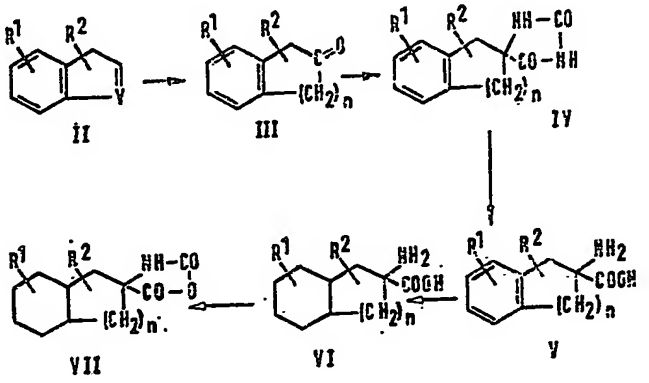
(c) m=p.

Silyl and silene groups can be removed readily by solvolysis, for instance with an alcohol or water.

As employed herein the term "lower alkyl" and the like are meant to include both branched and straight chain hydrocarbon moieties containing from one to seven carbon atoms. Typical examples of the compounds of this invention are: 6-(2-amino-hexahydro-2-indan-carboxamido)penicillanic acid; 6-(hexahydro-indan-2-amino-4-butyl-2-carboxamido)penicillanic acid; 6-(hexahydro-indan-2-amino-3-phenoxy-2-carboxamido)penicillanic acid; and 6-(2-amino-decahydro-3,6-dimethyl-2-naphthamido)penicillanic acid.

In the new penicillins of the present invention which are represented by structural formula (A), the acyl substituent has an asymmetric centre and two possible diastereoisometric forms as well as the racemic forms thereof. If a particular optical isomer is desired it can be readily prepared from an appropriate starting material of the same optical series obtained by a standard resolution procedure.

The new penicillins of the present invention can be prepared conveniently using N-carboxy anhydride which can be prepared by the preferred process depicted by the following reaction sequence:



where R, R^1, R^2 and n are as defined above and Y is —CH= or —CH_2—CH=.

The novel compounds of the invention may generally be prepared by reacting a suitable 4-substituted-2,5-oxazolidinedione (also known as an N-carboxy amino acid anhydride or NCA) with 6-amino-penicillanic acid (6-APA). Preferably, a solution of 6-APA and triethylamine is first prepared which is slightly acid (e.g. about pH 6). Thereafter the selected N-carboxy anhydride is added, and the reaction mixture stirred. The novel compounds of the invention, resulting from the reaction between 6-APA and the N-carboxy amino acid anhydride may then be recovered by conventional procedures such as filtration, concentration, water extraction and precipitation from organic solvents, as indicated.

The N-carboxy amino acid anhydrides suitable for preparing the new penicillins of Formula I above when n is 1; i.e. the 2-aminohexahydro-indane-2-carboxylic acid NCA's, may be prepared by a synthesis which starts with the preparation, from a selected indane, of the corresponding 2-indanone by the method described by Rose, Dorfman and Linfield in the Journal of Organic Chemistry 29, 1793, 1964. The hydantoin of the 2-indanone may then be prepared by the generally known method for reacting the 2-indanone with ammonium carbonate and potassium cyanide in an organic solvent. The resulting 2-indanone hydantoin may then be transformed to the 2-amino-indane-2-carboxylic acid by ring splitting hydrolysis, as by heating in the presence of barium hydroxide. The benzenoid moiety of the amino acid may be reduced to the corresponding hexahydro moiety by hydrogenation of said acid in an inert solvent, such as water in the presence of rhodium on carbon as catalyst, at a temperature within the range of about 10 to 60°C., as is also known to those skilled in the art. The NCA of the resulting 2-amino-hexahydroindane-2-carboxylic acid may be prepared by the phosgenation of said acid. The N-carboxy amino acid anhydrides suitable for use in the preparation of the novel penicillanic acid compounds of this invention may also be prepared by other known procedures such as those referred to or described, for example, in U.S.P. No. 3,194,802 of H. E. Alburn, N. H. Grant and H. Fletcher, 3rd.

The N-carboxyanhydrides suitable for preparing the new penicillins of Formula I wherein n is 2; i.e., 1,2,3,4,5,6,7,8,9,10-decahydronaphthalene-2-amino-2-carboxylic acid NCA's, may be prepared by a general synthesis similar to that set forth above, with merely the substitution of a selected 1,2,3,4-tetrahydronaphthalene for the indane starting material of the first synthesis.

The new penicillin compounds of the series defined above show desirable broad spectrum antibacterial activity and are useful as therapeutic agents for poultry and mammals in the treatment of infectious diseases caused by gram-positive and gram-negative bacteria, and are of surprisingly good activity particularly with respect to penicillin-resistant strains of staphylococci, by either parenteral or oral administration.

As parenteral antibiotics, they are particularly effective since, as referred to hereinbefore, they have low water-solubility which makes them useful in repository injectable dosage forms, without the necessity of forming salts of the new penicillins of Formula I with organic bases. As also referred to hereinbefore, the new penicillins of formula I are effective on oral administration because they are relatively acid resistant.

These compounds are, therefore, of value as antibacterial agents, nutritional supplements in animal feed; agents for the treatment of mastitis in cattle; and as therapeutical agents in poultry and mammals, in the treatment of infectious diseases caused by gram-positive and gram-negative bacteria, upon either parenteral or oral administration.

The penicillin compounds of the invention, in addition to being advantageously utilisable in their acid form, as noted hereinbefore; may also be used in the form of the therapeutically-active salts thereof, as will be understood by those skilled in the art. By way of example they can be used in the form of their non-toxic, biologically active salts, including non-toxic acid addition salts at an amino group, e.g. the hydrochloride, sulphate, fumarate, and maleate, or non-toxic metallic salts at the carboxy group, such as alkali or alkaline earth metal, e.g. sodium, potassium, calcium and aluminum salts and as organic salts, e.g. the ammonium salt and substituted ammonium salts, e.g. salts of such non-toxic amines as trialkylamines, including triethylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, N,N-alkylene diamines such as N,N'-dibenzylethylenediamine, N-(lower)alkylpiperidine, e.g. N-ethylpiperidine, dehydroabietylamine, N,N'-bisdehydroabietylethylenediamine and other amines which have been used to form salts with benzyl-penicillin, phenoxymethyl penicillin and the like. Separation of the desired product in the form of a salt is carried out by treatment with a base such as an alkali or alkaline earth metal salt of a relatively weak acid such as 2-ethylhexanoic acid.

When the compounds of this invention are employed in mammals, e.g. mice, rats, dogs, monkeys and the like, they may be administered orally or parenterally. Thus the invention also concerns pharmaceutical compositions comprising a compound of general formula I where Z is $-NH_2$ or a non-toxic salt thereof, in association with a pharmacologically acceptable carrier. The carrier can be solid or liquid or a mixture thereof and any suitable carrier known in the art can be used. The composition can be in the form of a suitable dosage form for example a solution or suspension or in a shaped solid form such as a tablet or capsule utilising conventional solvents, suspensoids or excipients.

Naturally, the dosage of these compounds will vary somewhat with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular subject under treatment, in general, the compounds of this invention are most desirably administered at dosage levels similar to those of commercially available penicillins at, for instance, a concentration level that is in the range of from about 10 to about 400 mg. per kilo per day, although as aforementioned variations will occur. However, this dosage range will generally afford effective results without causing any harmful or deleterious side effects.

The following examples are given by way of illustration:

EXAMPLE 1

6-(2-Amino-hexahydro-2-indancarboxamido)Penicillanic Acid

A. Preparation of 2-indanone

325 ml. of 99% formic acid, 34 ml. of water, and 70 ml. of 30% hydrogen peroxide were mixed and warmed to 35°C. over fifteen minutes. Freshly distilled indene (58.1 gms.) was added over 2 hours while maintaining a temperature of 34—36°C. with a cool water bath. The mixture was stirred an additional hour at 34—36°C. and then overnight at room temperature.

10.6 gms. of the heptahydrate of ferrous sulphate were added in 53 ml. of water to remove the active oxygen compounds and the solution was concentrated to 170 ml. *in vacuo*. A solution of 140 ml. of concentrated H_2SO_4 in 860 ml. of water was added and 200 ml. of distillate was steam distilled. The distillate was extracted with 3×100 ml. of methylene chloride. The extracts were combined and washed with 500 ml. of water, dried over Na_2SO_4, filtered and evaporated to an oil which crystallised. MP 57—59°C. 67%.

B. Preparation of 2-indanone hydantoin

2-Indanone, 22.5 gms. (0.17 moles), ammonium carbonate monohydrate 48.5 gms. (0.425 moles), and potassium cyanate 16.3 gms. (0.25 moles) were mixed in 210 ml. of formamide and heated in a pressure bomb at 100°C. overnight. The cooled

reaction was diluted with 600 ml. of water and acidified with concentrated HCl to a pH 2 with good ventilation. The precipitate was filtered, washed with water and dried. MP 255—7°C. Yield: 46—5 gms. wet. The material was purified by dissolving in 5% aqueous NaOH, extracting with ether, and acidifying. MP 260—262°C.

C. Preparation of 2-aminoindane-2-carboxylic acid

2-Indanone hydantoin 55.75 gms. (0.273 moles), barium hydroxide octahydrate 215 gms. (0.685 moles) and 300 ml. of water were heated in a bomb at 200°C. for 20 hours. The pressure reached 250 p.s.i. The hydrolysis mixture was acidified with concentrated HCl to pH 2, heated to boiling, treated with Darco G-60 and filtered. "Darco" is a Registered Trade Mark. 38 ml. of concentrated H_2SO_4 was added to the filtrate with stirring and the slurry was heated and filtered. The $BaSO_4$ precipitate was washed with hot water and the combined filtrates were evaporated to dryness. The residue was dissolved in 100 ml. of water and adjusted to pH 4.5 with aqueous NaOH and chilled. The product was dried. A second crop was obtained by concentrating the mother liquor.

Yield:	1st crop	12.2 gms.	MP 309—311°C.
	2nd crop	3.8 gms.	MP 291—293°C.
	Total	16.0 gms.	33%

D. Preparation of 2-amino-hexahydroindane-2-carboxylic acid

Hydrogenation of the 2-aminoindane-2-carboxylic acid was carried out by utilizing 17.7 g. of the amino acid, 8 ml. of concentrated HCl, and 2 g. of 5% rhodium on charcoal in 150 ml. of water in the Parr bomb, first at room temperature and then at 50°C. The system was filtered, and the filtrate was adjusted to pH 5.5 with NaOH. Crystals appeared after chilling. Yield: 12 g. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 64.56; H, 9.36; N, 7.68.

E. Preparation of N-carboxy-2-amino-hexahydroindane-2-carboxylic acid anhydride

N-carboxy-2-amino-hexahydroindane-2-carboxylic acid anhydride was prepared by treating 10 g. of the amino acid prepared in D. above in 500 ml. of dioxane with phosgene at 90° for 2½ hours. The clear solution was flushed with dry N_2 and evaporated to a semi-solid. This was dissolved in 75 ml. of warm ethyl acetate and crystallised by adding 75—100 ml. of hexane and chilling to 0°. Yield: 6.5 g. Calcd. for $C_{11}H_{15}NO_5$: C, 63.13; H, 7.22; N, 6.69. Found: C, 63.20; H, 7.15; N, 6.76.

F. Preparation of 6-(2-amino-hexahydro-2-indancarboxamido)penicillanic acid

A suspension of 5 g. of 6-APA in 50 ml. of water was adjusted to pH 6.2 with triethylamine. There was then added 4 g. of N-carboxy-2-amino-hexahydro-2-indancarboxylic acid anhydride, and the resulting suspension was stirred at 4° for 5 days. The suspension was filtered, and the collected material was washed with water, suspended in 150 ml. of ethyl acetate, and stirred at room temperature for 20 minutes. The insoluble material was collected by filtration, washed with ethyl acetate, and suspended in 100 ml. of water. After adjustment to pH 6.3 with triethylamine, the product was collected, washed with water, and dried. The yield was 5.3 g. Analysis: Calcd. for $C_{18}H_{27}N_3O_4S \cdot H_2O$: C, 51.7; H, 7.43; N, 10.0; H_2O, 8.6. Found: C, 51.7; H, 7.15; N, 9.99; H_2O, 8.1.

EXAMPLE 2

6-(2-amino-hexahydro-2-indancarboxamido)penicillanic acid

A mixture of 20 g. of 6-APA and 250 ml. of water was adjusted to pH 6.0 with triethylamine. After chilling to 4°, there was added 16 g. of N-carboxy-2-amino-hexahydro-2-indancarboxylic acid anhydride prepared as in Example 1, and stirring was carried out for 5 days. The suspension was filtered, and the precipitate was washed with 350 ml. of water and then dried under vacuum. The infra-red spectrum revealed the presence of residual N-carboxyanhydride; therefore, the product was washed by suspension in 500 ml. of ethyl acetate. The product was washed again with 400 ml. of water and was then filtered and dried giving 16.9 g. Analysis: Found: C, 51.7; H, 7.16; N, 10.2; H_2O, 8.39.

EXAMPLE 3

6-(2-amino-hexahydro-2-indancarboxamido)penicillanic acid was demonstrated to be superior to its aromatic analogue, 6-(2-amino-2-indancarboxamido)penicillanic acid, when tested by standard testing procedures against a series of organisms, with the results set forth in the following Table A:

Table A

Test Organism		Minimal Inhibitory Concentration, μg/ml 6-(2-amino-2-indancarboxamido) penicillanic acid	6-(2-amino-hexahydro-2-indancarboxamido) penicillanic acid
Bacillus subtilis	6633	1.95	0.244
Staphylococcus aureus	6538P	.976	0.488
Staphylococcus aureus	Smith	.976	0.488
Staphylococcus aureus	CHP	7.81	15.6
Staphylococcus aureus	53—180	31.3	7.81
Neisseria catarrhalis	8193	7.81	1.95
Escherichia coli	6880	250	3.90
Escherichia intermedia	65—1	—	125
Salmonella paratyphi	11737	31.3	15.6
Enterobacter aerogenes	884	7.81	0.488
Klebsiella	10031	—	125
Proteus vulgaris	6896	250	125
Herellea sp.	9955	125	250

Range tested: .0009—250 μg/ml

EXAMPLE 4

Following the procedure of Example 1, a series of N-carboxy amino acid anhydrides are prepared, and the latter, as given in Table B below, are respectively reacted with 6-APA to obtain the respective penicillin products also given in the Table.

Table B

N-Carboxy Amino Acid Anhydride	Penicillanic Acid Product
2-Amino-4-butyl-1,2,3,4,5,6,7,8-hexahydro-2-indancarboxylic acid N-carboxyanhydride	6-(1,2,3,4,5,6,7,8-hexahydro-indan-2-amino-4-butyl-2-carboxamido)penicillanic acid
2-Amino-3-phenoxy-1,2,3,4,5,6,7,8-hexahydro-2-indancarboxylic acid N-carboxyanhydride	6-(1,2,3,4,5,6,7,8-hexahydro-indan-2-amino-3-phenoxy-2-carboxamido)penicillanic acid
2-Amino-4-phenyl-1,2,3,4,5,6,7,8-hexahydro-2-indancarboxylic acid N-carboxyanhydride	6-(1,2,3,4,5,6,7,8-hexahydro-indan-2-amino-4-phenyl-2-carboxamido)penicillanic acid
2-Amino-1,2,3,4,5,6,7,8,9,10-decahydro-3,6-dimethyl-2-naphthoic acid N-carboxyanhydride	6-(2-Amino-1,2,3,4,5,6,7,8,9,10-decahydro-3,6-dimethyl-2-naphthamido)penicillanic acid
2-Amino-1,2,3,4,5,6,7,8,9,10-decahydro-7-ethoxy-2-naphthoic acid N-carboxyanhydride	6-(2-Amino-1,2,3,4,5,6,7,8,9,10-decahydro-7-ethoxy-2-naphthamido) penicillanic acid
2-Amino-1,2,3,4,5,6,7,8,9,10-decahydro-6-methoxy-2-naphthoic acid N-carboxyanhydride	6-(2-Amino-1,2,3,4,5,6,7,8,9,10-decahydro-6-methoxy-2-naphthamido)penicillanic acid

EXAMPLE 5

A mixture of 43.2 g. of 6-APA, 425 ml. of methylene chloride and 40.5 g. of triethylamine, was treated with 25.8 g. of dimethyldichlorosilane at 10—15°C. and the mixture refluxed gently for two hours. The mixture was treated at 0°C. with 16.6 g. of pyridine, and then 47.4 g. of 2-amino-hexahydroindane-2-carboxylic acid chloride hydrochloride was added portionwise over 20 minutes at 0°C. After stirring at 0°C. and finally at 20°C. for one hour, the reaction mixture was poured into 400 ml. of water, clarified by filtration, and adjusted to pH 5.4 by adding dilute sodium hydroxide solution.

After stirring overnight at 20°C., the product was collected by filtration, washed and dried to yield 51 g. of 6-(2-amino-hexahydro-2-indancarboxamido)-penicillanic acid.

EXAMPLE 6

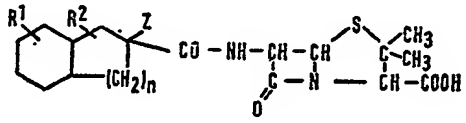
To 10.8 g. of 6-APA and 105 ml. of methylene chloride, 12.6 g. of triethylamine

and 6.7 g. of N,N-dimethylaniline were added. After stirring at reflux for one hour, the mixture was cooled and 10.8 g. of trimethylchlorosilane was added dropwise at 12—15°C. The mixture was refluxed for 45 minutes, cooled under nitrogen to 15°C., and 15 ml. of 0.8 M dimethylaniline dihydrochloride in methylene chloride was added. Thereafter, 11.8 g of 2-amino-hexahydroindane-2-carboxylic acid chloride HCl was added portionwise at −10°C. over 20 minutes. The mixture was stirred for an additional hour while the temperature rose to 20°C. The reaction mixture was poured into 100 ml. of cold water with stirring and the two-phase mixture clarified by filtration. Dilute sodium hydroxide solution was added to the filtrate at 5—10°C. to pH 5.4.

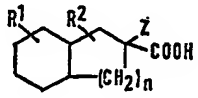
After stirring overnight at room temperature, the crystalline product was collected by filtration, washed with water and finally with acetone, and then dried at 45°C., to yield 13 g. of 6-2-amino-hexahydro-2-indancarboxamido)penicillanic acid.

WHAT WE CLAIM IS:—

1. A process for the preparation of a penicillin having the general formula



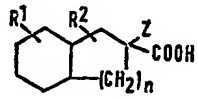
in which Z is an amino group or a protected amino group or an azido or nitro group R^1 and R^2 are hydrogen, lower alkyl, lower alkoxy, aryl or aryloxy and n is 1 or 2 or a salt thereof in which 6-aminopenicillanic acid or a functional derivative thereof is acylated with an acid of general formula



wherein R^1, R^2, Z and n are as defined above, or its functional derivative and, if desired, a protecting group is removed or an azido or nitro group Z is reduced to an amino group.

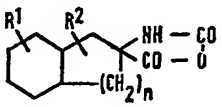
2. A process according to Claim 1 in which 6-aminopenicillanic acid or a salt or organosilyl or organosilenyl derivative thereof, is acylated.

3. A process according to Claim 2 in which the acylation is by reaction with an anhydride, mixed anhydride or N-carboxyanhydride or acyl halide of an acid of general formula



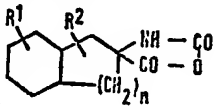
where Z, R^1, R^2 and n are as defined in Claim 1 or with the acid or its salt in the presence of a dehydrating or functionalising compound such as a carbodiimide or an N,N′-carbonyldiimidazole or alkoxyacetylene, any amino group Z being protected and the protecting group removed in known manner.

4. A process according to Claim 2 in which the acylation is by reaction with an N-carboxyanhydride of general formula



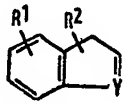
where R^1, R^2 and n are as defined in Claim 1.

5. A process according to Claim 1 in which 6-aminopenicillanic acid or a salt thereof is reacted with an N-carboxyanhydride of general formula

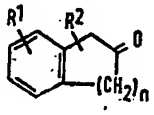


where R^1, R^2 and n are as defined in Claim 1.

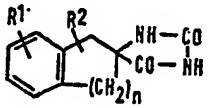
6. A process according to Claim 5 in which the N-carboxyanhydride is prepared by conversion in known manner of an indane of general formula



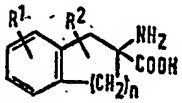
where R^1 and R^2 are as defined in claim 1 and Y is $—CH_2—CH=$ or $—CH=$ to one of general formula



wherein *n* is as defined in claim 1, which is reacted with ammonium carbonate and potassium cyanide to give a hydantoin of general formula



which in turn is hydrolysed to an acid of general formula



which is hydrogenated to the hexahydro acid which in turn is reacted with phosgene to produce the N-carboxy anhydride.

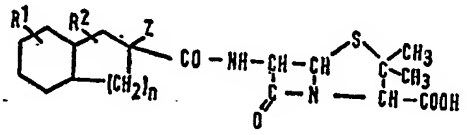
7. A process for the preparation of penicillins according to Claim 1 substantially as described herein and shown with reference to Examples 1 to 4.

8. A process for the preparation of penicillins according to Claim 1 substantially as described herein and shown with reference to Example 5 or 6.

9. A penicillin or its salt whenever prepared by a process according to any one of Claims 1 to 4 and 8.

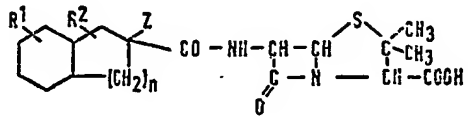
10. A penicillin or its salt whenever prepared by a process according to any one of Claims 5 to 7.

11. A penicillin having the general formula



in which Z is an amino group or a protected amino group or an azido or nitro group. R^1 and R^2 are hydrogen, lower alkyl, lower alkoxy, aryl or aryloxy and n is 1 or 2 or a salt thereof.

12. A penicillin having the general formula



in which R^1 and R^2 are hydrogen, lower alkyl, lower alkoxy, aryl or aryloxy, Z is amino and n is 1 or 2 or a salt thereof.

14. A penicillin according to Claim 12 in which n is 1.

15. 6-(2-Amino-hexahydro-2-indane carboxamido)penicillanic acid or a salt thereof.

16. A penicillin substantially as described herein with reference to any one of those listed in Table B or a salt thereof.

17. A pharmaceutical composition comprising a penicillin or its salt as claimed in any one of Claims 12 to 16 in association with a pharmacologically acceptable carrier.

18. A pharmaceutical composition comprising a penicillin as claimed in any one of Claims 12 to 16 in repository injectable form.

G. R. PORTER,
Agent for the Applicants,
c/o John Wyeth & Brother Limited,
Huntercombe Lane South,
Taplow, Maidenhead, Berkshire.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1973.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.